



UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/002,413 01/02/98 ALLEN R 311772000500

HM22/0921

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EXAMINER

WILSON, M

ART UNIT

PAPER NUMBER

1633

DATE MAILED:

09/21/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/002,413

Applicant(s)

ALLEN ET AL.

Examiner

Michael Wilson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 July 2001.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 33-64 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 33-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

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DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-24-01, paper number 26, has been entered.

Applicant's arguments filed 7-24-01, paper number 27, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 33-64 are pending and under consideration in the instant application as they relate to a method of administering cells to create an immunologically privileged site as originally elected.

Claim Objections

To expedite prosecution, the following claim language is recommended for claim 33: "administering a composition to a mammal, said composition comprising retinal pigment epithelial (RPE) cells and non-RPE cells, wherein said non-RPE cells are allogeneic to said mammal and produce a biologically active protein..." The type of molecule and therapeutic effect obtained are unclear at this time. Dependent claims should be amended to reflect the changes in claim 33.

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Claim Rejections - 35 USC § 112

2. Claims 33-64 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering a composition to mammal, said composition comprising retinal pigmented epithelial cells (RPE) and non-RPE, wherein said non-RPE cells are allogeneic to said mammal and produce a biologically active protein, such that a , does not reasonably provide enablement for administering RPE or RPE with non-RPE to obtain any therapeutic effect using any therapeutic protein/biologically active molecule in any disease as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The state of the art at the time of filing was that symptoms of Parkinson's disease were treated using RPE cells supported by a matrix transplanted into the brain of rats (Cherksey, see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). Cherksey did not expressly teach co-administering RPE and allogeneic non-RPE cells. However, Cherksey suggests transplanting a matrix having both RPE and allogeneic glial cells (column 9, line 2; column 11, line 37). In addition, RPE were known to provide "immune privilege" (Ye of record, 1993, Current Eye research, Vol. 12, pages 629-639, see page 629, column 1, line 1; page 630, column 2, line 24; last line of abstract and page 631, column 2, line 20), and non-RPE were transplanted in mammals to produce therapeutic molecules (Sigalla of record, Sept. 1, 1997, Human Gene Therapy, Vol. 8, pages 1625-1634; page 1626, column 2, 2nd

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and 3rd paragraphs; page 1628, column 1, 4th paragraph and column 2, 4th and 5th full paragraphs; Weber of record, 1997, J. Surg. Res., Vol. 69, pages 23-32; page 25, column 1, "Islet transplantation"; page 27, paragraph bridging columns 1 and 2; Fraser of record, 1995, Cell Transplantation, Vol. 4, pages 529-534).

However, the art at the time of filing did not teach the structure of a composition comprising RPE and allogeneic non-RPE administered to a mammal, define an "immune-privilege site" created by RPE, teach that such a site can protect allogeneic non-RPE from the immune system or allow non-RPE to grow and secrete biologically active molecules. Therefore, it was unpredictable at the time of filing how to use a composition comprising RPE and allogeneic non-RPE to create an "immune-privileged site" wherein the non-RPE secrete therapeutically effective amounts of a biologically active molecule.

The specification contemplates treating a number of diseases (page 1, line 23; page 3, line 26; page 5, line 31), suggests genetically engineering RPE to produce any of a number of therapeutic proteins (page 8, line 31), and suggests delivering the RPE to any of a number of tissues (page 15, line 7). The specification also contemplates co-administration of RPE with cells supplying therapeutic molecules (page 4, line 20). Co-administration can be as a single composition or as separate compositions (page 4, line 23). Co-administration as defined in the specification encompasses administering RPE cells alone because RPE "supply therapeutic molecules" such as dopamine and because the definition does not require that the cells that "supply therapeutic molecules" are non-RPE. Cells that can be co-administered with RPE are

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neural cells, endocrine cells, muscle cells and other cells that produce a functionally active therapeutic molecule (sentence bridging pages 6 and 7).

The specification demonstrates isolating and culturing fetal RPE *in vitro* (pages 16-20) obtaining FasL expression by RPE and apoptosis of thymocytes contacted with the RPE *in vitro* (pages 21-27). The specification does not teach the structure of a composition comprising RPE and allogeneic non-RPE administered to a mammal, define an “immune-privilege site” created by RPE, teach that such a site can protect allogeneic non-RPE from the immune system or allow non-RPE to grow and secrete biologically active molecules. Specifically, the specification does not provide any guidance on how to use pancreatic islet of Langerhans cells (claim 22). Merely suggesting administering RPE and non-RPE and listing the possible combination of parameters is inadequate to enable one of skill in the art to use the claimed invention to create an “immune privileged site” or produce a therapeutically effective amount of a biologically active compound from the non-RPE in such a site. Therefore, the specification does not overcome the unpredictability in the art by teaching how to use a composition comprising RPE and allogeneic non-RPE to create an “immune-privileged site” or to secrete therapeutically effective amounts of a biologically active molecule from non-RPE in such a site.

Specifically, the specification does not enable administering insulin-producing cells (claim 62), Langerhans cells (claim 63) or any other cells producing neurotransmitters (claims 34 and 55), hormones (claims 35 and 56), cytokine inhibitors (claims 36 and 57) or growth factors, cytokines, or differentiation factors (claims 37 and 58) to treat a neurological (claims 51 and 52),

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metabolic (claims 51 and 53), cardiac, endocrine, hepatic, pulmonary or immunological diseases (claim 51), or non-RPE transfected with a vector encoding a protein (claims 39 and 40) as broadly claimed for reasons of record.

Applicants argue that the specification provides examples of diseases responsive to a biologically active molecule, of biologically active molecules that are therapeutic and of cells that produce such molecules. Such lists are not adequate to enable one of skill in the art how to use a composition comprising RPE and non-RPE such that the non-RPE secrete a therapeutically effective amount of biologically active molecule. Applicants are claiming that the allogeneic non-RPE are protected in an "immune-privileged site" created by the RPE and produce a therapeutically effective amount of a biologically active molecule. Applicants have not shown any evidence indicating that the allogeneic non-RPE survive in the "immune-privileged site" as the site may not provide conditions for non-RPE survival *in vivo*. Applicants have not shown any evidence indicating the allogeneic non-RPE are not attacked by the immune system of the mammal which would recognize allogeneic cells as foreign. Applicants have not shown any evidence that the biologically active molecule is secreted from the "immune-privileged site" which may be incapable of allowing molecules to be secreted from the site. Applicants have not provided any evidence that the molecule is secreted to levels that are therapeutic. Applicants have not demonstrated obtaining any therapeutic effect *in vivo* using a composition comprising RPE and non-RPE. Given the unpredictability in the art taken with the teachings in the specification, it would have required one of skill undue experimentation to determine the parameters required to

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administering RPE and allogeneic non-RPE that produce a biologically active molecule to a mammal, such that the biologically active molecule is secreted in an amount effective to sustain a therapeutic effect as claimed.

3. Claims 33-53 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 is indefinite because the metes and bounds of "co-administering" cannot be determined. Claim 49 states co-administration occurs in a single composition. Claim 50 states co-administration occurs as separate compositions. The definition of co-administering is administration of RPE with cells supplying therapeutic molecules (page 4, line 20). The specification states co-administration can be as a single composition or as separate compositions (page 4, line 23). Thus, it appears that the claims encompass administering separate compositions at separate times. However, if the cells are administered as separate compositions, how far apart in time can the cells be administered and still be considered "co-administered?" "Co-administered" implies the RPE and non-RPE cells are administered at the same time, but is unclear how one would administer RPE and non-RPE cells to one site in a mammal as separate compositions and at the same time. Administering separate compositions at separate times to the same site is contrary to the art accepted meaning of co-administering and is indefinite because it is unclear how far apart in time the separate compositions can be administered and still be considered "co-administered."

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Claim 33 is indefinite because the phrase “immune-privileged site” indefinite because the metes and bounds of what applicants consider an immune-privileged site cannot be determined (see 112/2nd). The specification and the art at the time of filing did not define the metes and bounds of an “immune-privileged site.” When is a site considered to be “immune-privileged?” What is an “immune-privileged site” within an immune-privileged site such as the brain? What is the structure/function of an “immune-privileged site” in the brain as compared to other tissue? Are the allogeneic cells protected from the immune system for a certain period of time? If so, how long must the allogeneic non-RPE be protected from the immune system of the host for the composition to be considered to have created an “immune-privileged site?” Thus, one of skill would not be able to determine when the composition had creating an “immune-privileged site.”

Claim 33 is indefinite because “the biologically active molecule that is deficient in the disease” lacks antecedent basis in claim 33. It is not clear that the mammal has a disease or is deficient in a particular molecule. It is not clear that the disease is caused by such a deficiency.

Claim 33 is indefinite because “said non-RPE cell population” lacks antecedent basis.

Claim 40 is indefinite because the it is unclear if the “biologically active protein” is the “biologically active molecule.” Changing claim 33 to “biologically active protein” is recommended.

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Claim Rejections - 35 USC § 103

4. Claims 33-38, 41-49, 51-61 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) for reasons of record.

Cherksey taught treating symptoms of Parkinson's disease using $300-3.75 \times 10^5$ RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). Cherksey does not teach co-administering RPE and non-RPE cells. However, Cherksey suggests transplanting a matrix having both RPE and glial cells attached (column 9, line 2) and that the cells may be allogeneic to the host (column 11, line 37). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer RPE and glial cells wherein the glial cells are allogeneic to the host as taught by Cherksey. One of ordinary skill in the art at the time the invention was made would have been motivated to add glial cells to the RPE as suggested by Cherksey and to treat neural disorders in the brain.

Applicants argue that Cherksey is silent with regard to the relationship of the glial cells to the RPE and/or the host. Applicants argument is not persuasive as Cherksey states the cells of the invention may be allogenic in relationship to the host (col. 11, line 38). As glial cells are encompassed by Cherksey's invention, the glial cells may be allogenic in relationship to the host. Since the RPE contemplated by Cherksey may be autologous, the glial cells would inherently be

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allogeneic to the RPE. Thus, Cherksey obviates non-RPE that allogeneic to the host or to the RPE.

Applicants argue the claim requires making an immune-privileged site while Cherksey administers cells into a pre-existing immune-privileged site. Applicants argument is not persuasive because the phrase “creating an immune privileged site in a mammal by...” is an intended use and is not clearly a result of co-administering RPE cells. However, the metes and bounds of what applicants consider an immune-privileged site cannot be determined (see 112/2nd).

Applicants argue the method does not encompass co-administering the cells to the brain which is already an immune-privileged site. Applicants argument is not persuasive because the claims are not limited to administering the cells to a site that is not already an immune-privileged site. Can the method not be performed in the brain? If it can, what is an “immune-privileged site” within an immune-privileged site? What is the structure/function of an “immune-privileged site” in the brain as compared to other tissue? When is a site considered to be “immune-privileged?” Furthermore, without evidence to the contrary, co-administering RPE and glial cells that are allogeneic to the host to the brain as taught by Cherksey inherently creates an “immune-privileged site” in the host as claimed.

5. Claims 33, 39 and 40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (Cherksey U.S. Patent 5,618,531, April 8, 1997) in view of Goldstein (Goldstein et al., U.S. Patent 5,300,436, April 5, 1994) for reasons of record.

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Cherksey taught treating symptoms of Parkinson's disease using $300-3.75 \times 10^5$ RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). Cherksey does not teach co-administering RPE and non-RPE cells. However, Cherksey suggests transplanting a matrix having both RPE and glial cells attached (column 9, line 2) and that the cells may be allogeneic to the host (column 11, line 37). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer RPE and glial cells wherein the glial cells are allogeneic to the host as taught by Cherksey. One of ordinary skill in the art at the time the invention was made would have been motivated to add glial cells to the RPE as suggested by Cherksey and to treat neural disorders in the brain. Cherksey did not teach transfecting the RPE with a nucleic acid sequence encoding a biologically active protein. However, Goldstein taught administering cells transfected with a vector encoding tyrosine hydroxylase to the brain to treat symptoms associated with Parkinson's disease (column 4, line 50; column 17, line 49). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer RPE and glial cells that were allogeneic to the host as taught by Cherksey and the method of treating Parkinson's using cells transfected with tyrosine hydroxylase as taught by Goldstein. Motivation is provided by Goldstein by stating RPE can be transfected with tyrosine hydroxylase (column 15, lines 26-61, see line 59). Thus, it would have been obvious to one of skill in the art at the time of filing to

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transfect either the RPE or the glial cells with a vector encoding tyrosine hydroxylase to treat symptoms of Parkinson's disease.

Applicants argue Goldstein does not address the deficiencies of Cherksey. Applicants argument is not persuasive for reasons cited above.

Claim 50 appears to be free of the prior art of record because the prior art of record does not teach or suggest administering RPE and non-RPE separately in an amount effective to sustain a therapeutic effect. Claims 62 and 63 appear to be free of the prior art of record because the prior art of record did not teach or suggest combining RPE and insulin-producing cells such as pancreatic islet of Langerhans cells as claimed.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 305-0196.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL C. WILSON
PATENT EXAMINER